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ORIGINAL ARTICLE

Impact of epicardial adipose tissue on diastolic dysfunction in patients with chronic coronary syndrome and preserved left ventricular ejection fraction

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Abstract

Aims

This study aims to investigate the association between left ventricular diastolic dysfunction (LVDD) and epicardial adipose tissue (EAT) accumulation in patients with chronic coronary syndrome (CCS) and preserved left ventricular ejection fraction (LVEF).

Methods and results

The study included 314 patients with preserved LVEF who underwent coronary computed tomographic angiography (CCTA) and thoracic tissue Doppler echocardiography (TTDE). The EAT volume was measured using CCTA. LVDD was categorized into three groups: absent LVDD, undetermined LVDD, and LVDD. Multivariate logistic regression analysis was performed to assess the association between the clinical parameters, TTDE and CCTA findings, and LVDD. Patients (mean age: 66 ± 13 years; 52% men) were divided into LVDD present (30 patients, 9.6%), LVDD absent (219 patients, 69.7%), and LVDD undetermined (65 patients, 20.7%) groups. CCTA showed that patients with LVDD had a significantly higher coronary artery calcium (CAC) score and % plaque volume (%PV) than those without LVDD, whereas the prevalence of obstructive coronary artery disease was comparable between the groups. The EAT volume index correlated with each LVDD diagnostic component, except for tricuspid regurgitation velocity. A multivariate model showed that age [odds ratio (OR), 1.13; $P < 0.001$] and EAT volume index (OR, 1.02; $P = 0.038$) were independently associated with LVDD, even after adjusting for left ventricular mass index (OR, 1.05; $P = 0.005$). There was no significant association between the CAC score and %PV or LVDD.

Conclusion

This study demonstrated that EAT volume index and left ventricular mass index were robust predictors of LVDD; however, there was no independent association between coronary atherosclerotic disease burden and LVDD.

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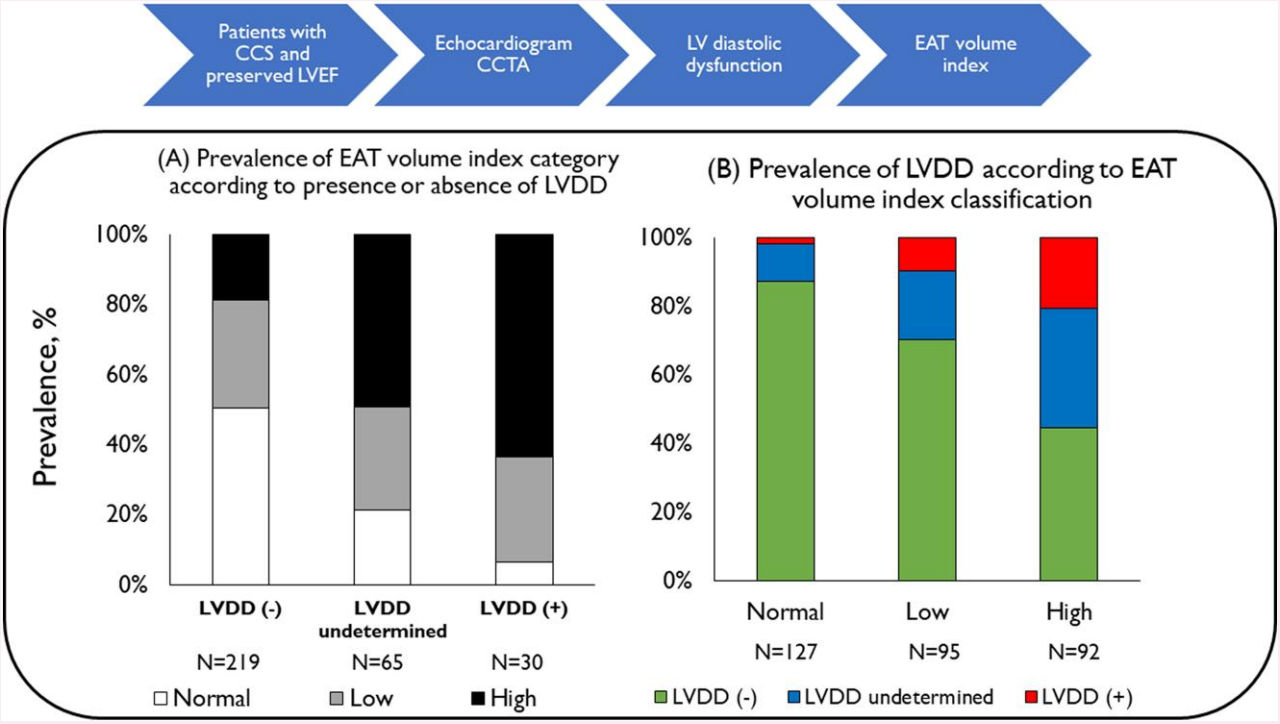
Graphical Abstract



Prevalence of EAT volume index category according to presence or absence of LVDD (*A*) and prevalence of LVDD according to EAT volume index classification (*B*).

Keywords coronary computed tomographic angiography • atherosclerosis • epicardial adipose tissue • left ventricular diastolic function • echocardiography

Introduction

Chronic coronary syndrome (CCS) is a progressive atherosclerotic disease that is concomitant with structural and functional alterations of the heart.[1] Left ventricular diastolic dysfunction (LVDD) plays a pivotal role in the pathophysiology of progression to heart failure (HF) with and without preserved left ventricular (LV) ejection fraction (EF).[2] In addition, LVDD serves as a marker of subclinical cardiac dysfunction even in patients without HF.[3] Studies in both human and animals have consistently demonstrated that LVDD can be caused by aging, LV hypertrophy, and ischaemia.[4–6] However, the underlying mechanism causing LVDD in CCS patients remains unclear.

Cardiac fibrosis is a central mediator of progression to HF, because the cardiac interstitial tissues undergo dynamic alterations that impact cardiac function.[7] Recent studies have demonstrated that epicardial adipose tissue (EAT) plays a major role in cardiac fibrosis through immune cell activation, providing critical insight into the pathophysiology of LVDD.[8] Coronary computed tomographic angiography (CCTA) enables quantification of EAT volume together with the extent and severity of coronary atherosclerosis.[8,9] In a previous study using CCTA, we demonstrated that EAT volume is associated with subclinical LV dysfunction, as assessed by LV longitudinal strain in patients with CCS.[9] However, a detailed understanding of the mechanisms linking the EAT and LVDD is lacking for patients with CCS and preserved left ventricular ejection fraction (LVEF). In the present study, we aimed to investigate the association among EAT volume, coronary atherosclerotic disease, and LVDD in patients with CCS and preserved LVEF.

Methods

Study participants

This retrospective, single-centre, observational study included symptomatic patients with CCS who underwent CCTA and thoracic tissue Doppler echocardiography (TTDE) between April 2017 and November 2020 at the Fujiikai Kashibaseiki Hospital, Japan. Patients with a <50% reduction in LVEF, atrial fibrillation, a history of coronary artery bypass grafting, open-heart surgery, a history of coronary revascularization, LV asynergy, valvular heart disease of more than moderate severity, or poor image quality were excluded. A total of 314 patients who underwent CCTA and TTDE were included in this study (*Figure 1*). The Ethics Committee of Kashibaseiki Hospital, Japan approved the study protocol (Ethical Approval Number 2023–6). The requirement for written informed consent was waived by the institutional review board because of the retrospective study design. In addition, an opt-out process was conducted that gave patients the option to refuse or permit the use of anonymized patient data, including clinical information, laboratory test results, TTDE, and CCTA imaging. The study was conducted in accordance with the principles of the Declaration of Helsinki.

TTDE measurement

The TTDE examination was conducted 2 weeks before the CCTA examination in all patients. All TTDE examinations were performed in a standard manner by experienced cardiac echosonographers using a Vivid S70 instrument (General Electric, Milwaukee, WI, USA) under continuous electrocardiogram monitoring. The LVEF was calculated using apical two-chamber and four-chamber views. Left atrial volume (LAV) was measured using the temporal frame just prior to mitral valve opening on the four-chamber

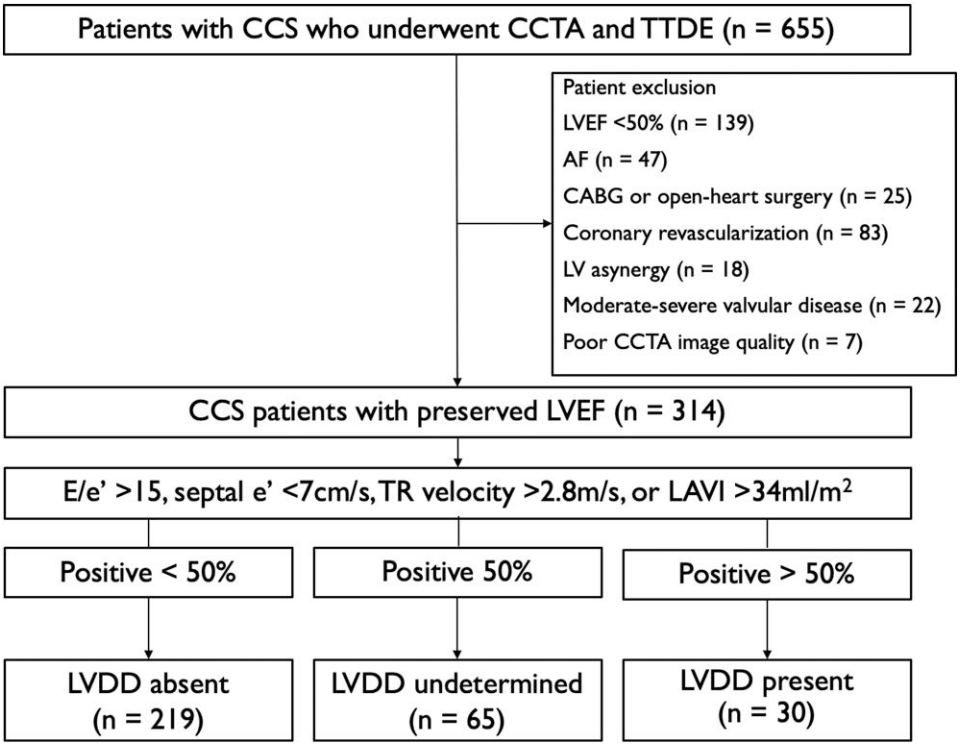


Figure 1 Study population flow chart.

view and the two-chamber view and was indexed to body surface area to calculate the LAV index (LAVI). Mitral inflow was assessed using pulsed-wave Doppler to measure early (*E*) and late (*A*) peak velocities. The early diastolic (*e′*) and late diastolic (*a′*) mitral annular velocities were also measured using tissue Doppler imaging of the septal wall, which provided the ratio of *E* to *e′* (*E*/*e′*) and LAVI/*a′* (*Figure 2A and B*). Tricuspid regurgitation (TR) velocity was assessed using continuous-wave Doppler. According to the American Society of Echocardiography (ASE) guidelines (Algorithm A), LVDD was categorized into three groups: LVDD (−), LVDD-undetermined, and LVDD (+).[2] In this study, we employed the cut-off value of *E*/*e′* > 15 as a parameter of LVDD because we used septal *e′*.[3] All echocardiographic measurements were performed based on the recommendations of the ASE by two independent cardiologists who were blind to the patient demographics or CCTA results.

CCTA acquisition and analysis

All patients underwent CCTA using a 320-row MDCT instrument (Aquilion ONE/NATURE Edition; Canon Medical Systems, Inc., Tochigi, Japan). CCTA scans were conducted with electrocardiogram-triggered prospective gating at a tube voltage of 120 kV, detector collimation of 0.5 × 320 mm, gantry rotation time of 350 ms, and a tube current of 130–600 mA. A β-blocker and nitrates were given to control heart rate and coronary artery dilation. A bolus tracking method was used for image acquisition. A non-ionic contrast medium of 270 mg I/kg (iopamidol, 370 mg I/mL; Bracco, Milan, Italy) was administered using a power injector at a rate of 3.3–4.9 mL/s, and saline was injected at the same rate. Coronary artery calcium (CAC) scores were assessed using continuous images of 3 mm thickness. The CAC scores were classified into five categories according to the Agatston method: 0, 0–10, 10–100, 100–400, or >400. The total calcium score was calculated by adding the CAC scores measured in the left main, left ascending, left circumflex, and right coronary arteries.

For the CCTA image analysis, 3D volume-rendered images, linear and telescopic curve planar reconstructed images, and cross-sectional multiplanar reconstructed images were automatically generated using Synapse Vincent software (Fujifilm Corporation, Tokyo, Japan). Coronary artery diameter stenosis was reported by two observers (K.O. and H.I.). Obstructive coronary artery disease (CAD) was defined as ≥50% stenosis of one or more major epicardial coronary arteries and/or ≥50% stenosis of the left main coronary trunk. Non-obstructive CAD was defined as the presence of atherosclerotic plaques with <50% stenosis in one or more major epicardial coronary arteries. Segment stenosis score (SSS) and segment involvement score (SIS) were used to assess the extent and severity of CAD.[10]

Visceral fat analysis

The EAT was analysed on axial views with a 0.5 mm slice thickness in contrast-enhanced CT images using SYNAPSE VINCENT software.[9,11] The upper limit of the slice was set at the bifurcation of the pulmonary artery trunk, whereas the lower limit was set at the last slice containing any structure of the heart. EAT was defined as adipose tissue identified with CT attenuation values ranging from −190 to −30 HU within the pericardial sac (*Figure 2C*). In each plane, the software automatically detected a smooth, closed pericardial contour as the region of interest, the EAT volume was calculated as the sum of the EAT areas in each slice. The EAT volume index was calculated as EAT volume (mL) divided by body surface area (m^2). In addition, abdominal visceral fat area (VFA) was measured at the level of L2 and L3 in non-contrast-enhanced CT images.

To investigate the association between LVDD and EAT volume index, we further categorized patients into three groups according to the EAT volume index: normal (<68.1 mL/m^2), low (68.1–89.4 mL/m^2), and high (> 89.4 mL/m^2). The normal value for the EAT volume index was defined as <68.1 mL/m^2 based on previous reports by Shmilovich *et al.*,[12] investigating the 95th percentile definition of the upper limit of the normal EAT volume index.

Statistical analysis

All statistical analyses were performed using SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables

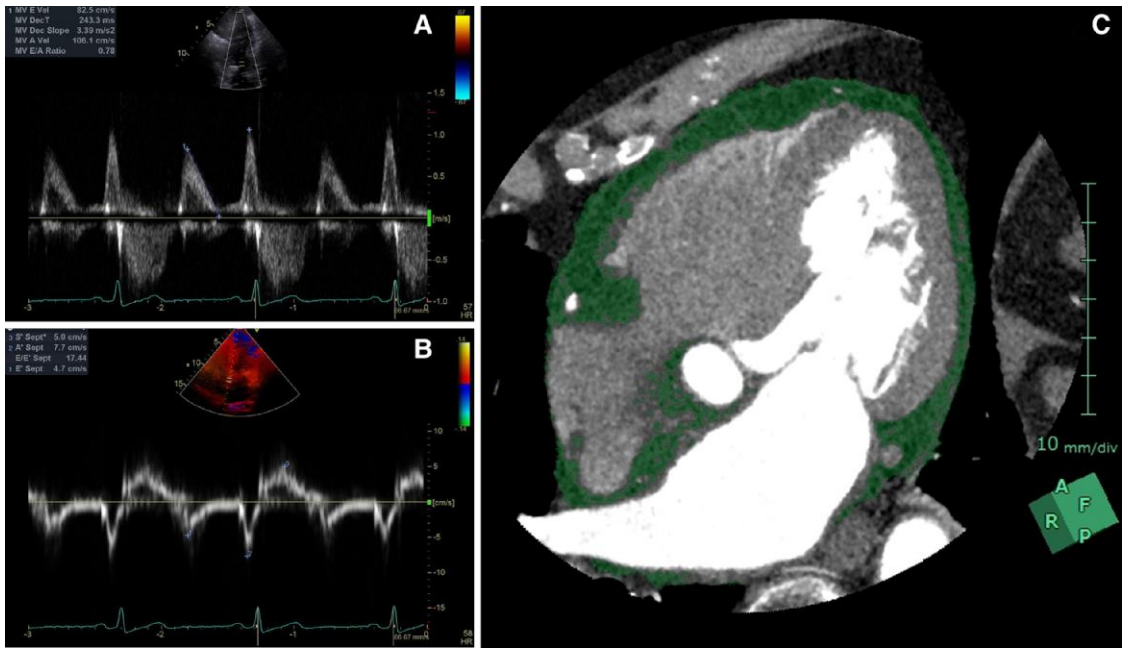


Figure 2 Measurements of echocardiographic LVDD parameters and EAT volume using coronary computed tomography angiography. (*A*) Mitral inflow assessed by pulse-wave Doppler shows the early (*E*) and late (*A*) peak velocities. (*B*) Early diastolic mitral annular velocity (e′) was measured using tissue Doppler imaging in the septal wall, showing the ratio of *E* to e′ (*E*/e′). (*C*) EAT was measured on axial views with a 0.5 mm slice thickness in contrast-enhanced CT images.

were expressed as mean ± standard deviation, and non-normally distributed continuous variables were expressed as medians (interquartile range). Categorical variables are expressed as frequencies (percentages). Patient characteristics and CCTA and TTDE findings were compared using one-way analysis of variance (ANOVA). Spearman's correlation was used to assess the relationship between EAT volume index and TTDE parameters. Multivariate logistic regression analysis was performed to evaluate the association between the clinical parameters, TTDE and CCTA findings, and LVDD. Model 1 was adjusted for age and sex, Model 2 was adjusted for age and LV mass index, Model 3 was adjusted for age and log (CAC + 1), and Model 4 was adjusted for age and total % plaque volume (%PV). $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics and echocardiographic parameters of the study patients

In total, 314 patients who underwent CCTA and TTDE were included in this study. The mean age was 66 ± 13 years (range: 40–85 years), and 52% of the population were men. The patient demographics are summarized in *Table 1*. Of the 314 patients, LVDD was diagnosed in 30 (9.6%), non-LVDD in 219 (69.7%), and undetermined LVDD in 65 (20.7%) (*Figure 1*). There were no significant differences in body mass index or prevalence of diabetes between the groups. Patients with LVDD were older and had a higher prevalence of hypertension and dyslipidaemia than those without LVDD; there were also more male patients with LVDD than female patients. The TTDE measurements and number of echocardiographic components used to diagnose LVDD are shown in *Table 2*. The LVEF and LV dimensions were similar across the groups; however, in addition to the components of the LVDD diagnostic parameters, a higher LV mass index was observed in LVDD (+) and LVDD-undetermined patients than in those without LVDD.

Association of coronary atherosclerosis and EAT with LVDD

The CCTA characteristics of each group are shown in *Table 2*. Patients with LVDD had significantly higher CAC scores and %PV than those without LVDD, whereas the prevalence of obstructive CAD was comparable across the groups. There were no statistically significant differences in CAD severity or extent (SIS and SSS) among the three groups.

The mean EAT volume and abdominal VFA index were 76 ± 25 and 61 ± 29 cm^2/m^2, respectively. The greatest EAT volume and VFA indices were observed in patients with LVDD, followed by those with undetermined LVDD, and those without LVDD. The *Graphical Abstract* (*A* and *B*) illustrates the correlation between the EAT volume index and each LVDD diagnostic component. Spearman's correlation tests demonstrated that EAT volume index was correlated with septal e′ ($\rho = -0.42$, $P < 0.001$), *E*/e′ ($\rho = 0.33$, $P < 0.001$), and LAVI ($\rho = 0.35$, $P < 0.001$), except for TR velocity ($\rho = 0.09$, $P = 0.097$). In addition, EAT volume index was also significantly correlated with LV mass index ($\rho = 0.33$, $P < 0.001$) and LAVI/*a*′ ($\rho = 0.38$, $P < 0.001$). In the comparison between LVDD-undetermined and LVDD patients (+), there were significant differences in EAT volume index and LAVI/*a*′.

LVDD and EAT

In LVDD (−) patients, 127/219 (58%) had a normal EAT volume index (*Graphical Abstract A*). For prevalence of the abnormal LVDD parameters, the LVDD (−) patients ($n = 219$) had *E*/e′ > 15, septal e′ < 7 cm/s, TR velocity > 2.8 m/s, and LAVI > 34 mL/mm^2 in 0 (0%),

Table 1 Patient characteristics

	LVDD (−) $n = 219$	LVDD undetermined $n = 65$	LVDD (+) $n = 30$	*P*-value
Age, years	63 (13)	73 (9)	78 (7)	<0.001
Male, *n* (%)	123 (56%)	27 (42%)	12 (40%)	0.048
BMI, kg/mm^2	23.7 (3.9)	24.5 (4.4)	23.3 (3.2)	0.280
Hypertension, *n* (%)	149 (68%)	57 (88%)	27 (90%)	0.001
Diabetes, *n* (%)	48 (22%)	15 (23%)	6 (20%)	0.944
Dyslipidaemia, *n* (%)	140 (64%)	52 (80%)	22 (73%)	0.041
Systolic BP, mmHg	141 (22)	142 (23)	149 (24)	0.119
Heart rate, bpm	75 (12)	76 (17)	76 (19)	0.850
Current or past smoker, *n* (%)	31 (14%)	8 (12%)	4 (13%)	0.967
Laboratory parameters				
Triglyceride, mg/dL	143 (105)	151 (64)	120 (82)	0.400
HDL-C, mg/dL	64 (20)	57 (18)	66 (18)	0.047
LDL-C, mg/dL	123 (33)	116 (43)	121 (34)	0.478
Fasting plasma glucose, g/dL	118 (38)	121 (42)	115 (26)	0.784
Glycosylated haemoglobin A1c, %	6.0 (0.9)	6.1 (1.2)	6.0 (0.8)	0.697
CRP, mg/L	1.9 (4.2)	4.3 (7.7)	5.2 (12)	0.008
eGFR, mL/min/1.73mm^2	71 (14)	65 (17)	57 (16)	<0.001
Medications				
ACE inhibitor or ARB, *n* (%)	47 (21%)	19 (29%)	16 (53%)	0.001
Calcium channel blocker, *n* (%)	62 (28%)	22 (34%)	15 (50%)	0.051
β-blocker, *n* (%)	12 (5.4%)	5 (7.7%)	6 (20%)	0.016
Statins, *n* (%)	51 (23%)	25 (38%)	9 (30%)	0.050
Oral anti-diabetic drugs, *n* (%)	26 (12%)	7 (11%)	5 (17%)	0.702

Values are given as mean (standard deviation) or number (%).
ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular flow rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

104 (47.4%), 2 (0.91%), and 15 (6.8%), respectively, demonstrating abnormal e′ was frequently found even in LVDD (−) patients. In contrast, most patients with a normal EAT volume index had no LVDD (−) (*Graphical Abstract B*).

Supplementary data online, *Tables S1* and *S2* show clinical characteristics and TTDE and CCTA findings in patients stratified by the EAT volume index category. Comparing the associations of LVDD classification with the EAT volume index category, 87.4% of the patients with a normal EAT volume index had no LVDD, while the prevalence of no LVDD decreased according to the severity of the EAT volume index category (*Figure 3*). Furthermore, we observed statistically significant differences in LVDD parameters, including septal e′, *E*/e′, LAVI, and LAVI/*a*′, among groups stratified by EAT volume index category (one-way ANOVA, $P < 0.001$; Supplementary data online, *Figure S1*).

Predictors of LVDD

Table 3 shows the multivariate logistic regression model adjusted for covariates. In the multivariate model adjusted for sex, age (odds ratio, 1.13; $P < 0.001$) and EAT volume index (odds ratio, 1.03; $P = 0.003$) were independent predictor of LVDD (Model 1 in *Table 3*). Age (odds ratio, 1.13; $P < 0.001$) and EAT volume index (odds ratio, 1.02; $P = 0.038$) were independently associated with LVDD even after adjusting for LV mass index (odds ratio, 1.05; $P = 0.005$; Model 2 in *Table 3*). Furthermore, age and EAT volume index were independently associated with LVDD, even after adjusting for CAC score (Model 3 in *Table 3*) and %PV (Model 4 in *Table 3*). In contrast, there was no significant association between the CAC score, %PV, and LVDD (Models 3 and 4 in *Table 3*).

Discussion

This study investigated the association between coronary atherosclerosis, ectopic fat deposition, and LVDD, as diagnosed according to the ASE guidelines, in patients with CCS who underwent TTDE and CCTA. Increases in EAT volume index and LV mass were robust predictors of LVDD, whereas there was no independent association between coronary atherosclerotic disease burden and LVDD. The majority of patients with normal EAT volume index was found to have LVDD (−). Furthermore, patients with undetermined LVDD had a higher EAT volume than those without LVDD, suggesting that the EAT volume can serve as a marker for LVDD.

e′ as a marker of LVDD

Kuznetsova *et al.*[13] demonstrated that e′ rather than *E*/e′ is a predictor of fatal and non-fatal cardiovascular events in the general population. Lundorff *et al.*[14] showed that e′ was independently associated with adverse cardiovascular outcomes in women from the general population. In outpatients with normal LVEF and without HF, Nistri *et al.*[15] demonstrated that only e′ is an independent and incremental predictor of outcomes. These findings indicate that e′ rather than *E*/e′ is a more useful prognostic marker for cardiovascular events in asymptomatic individuals.

Table 2 Thoracic tissue Doppler echocardiography and coronary computed tomographic angiography findings

	LVDD (−) $n = 219$	LVDD undetermined $n = 65$	LVDD (+) $n = 30$	*P*-value
TTDE parameters				
LVDD, mm	45 (5.0)	46 (5.8)	46 (5.1)	0.417
LVDS, mm	28 (4.5)	28 (5.2)	28 (5.7)	0.732
LVEF, %	62 (4.0)	61 (8.8)	62 (8.9)	0.836
LV mass index, g/m^2	73 (17)	85 (20)	91 (19)	<0.001
E wave velocity, cm/s	66 (17)	62 (16)	81 (14)	<0.001
A wave velocity, cm/s	70 (17)	82 (17)	92 (24)	<0.001
Septal e′, cm/s	7.2 (2.2)	5.1 (1.3)	4.6 (1.1)	<0.001
Septal *E*/e′ ratio	9.5 (2.3)	13 (4.2)	18 (4.2)	<0.001
LAVI, mL/m^2	24 (7.7)	37 (11)	42 (10)	<0.001
Tricuspid regurgitation velocity, m/s	2.0 (0.6)	2.1 (0.7)	2.5 (0.5)	<0.001
a′, cm/s	9.9 (2.0)	8.9 (2.0)	9.1 (2.4)	0.003
LAVI/*a*′	2.5 (0.9)	4.3 (1.7)	4.9 (2.0)	<0.001
CCTA parameters				
CAC score, HU	159 (441)	157 (285)	445 (595)	0.003
CACS 0, *n* (%)	105 (48%)	21 (32%)	4 (13%)	<0.001
CACS 1–100, *n* (%)	55 (25%)	25 (38%)	8 (27%)	0.108
CACS 101–400, *n* (%)	40 (18%)	11 (17%)	9 (30%)	0.272
CACS >400, *n* (%)	19 (8.6%)	8 (12%)	9 (30%)	0.003
Stenosis severity on CCTA				
Non-obstructive CAD, *n* (%)	78 (36%)	25 (38%)	12 (40%)	0.264
Obstructive CAD, *n* (%)	56 (26%)	12 (18%)	7 (23%)	0.760
SIS	2.5 (2.6)	2.4 (2.4)	2.9 (3.2)	0.592
SSS	5.4 (6.4)	5.0 (5.3)	7.4 (9.0)	0.240
Coronary plaque volume, %	45 (5.0)	46 (7.2)	48 (6.5)	0.038
Adipose tissue parameters				
Abdominal VFA index, cm^2/mm^2	59 (28)	66 (32)	71 (29)	0.040
EAT volume index, mL/mm^2	69 (22)	90 (25)	98 (21)	< 0.001

Values are given as mean (standard deviation) or number (%).
CAC, coronary artery calcium; CAD, coronary artery disease; EAT, epicardial adipose tissue; CCTA, coronary computed tomographic angiography; LAVI, left atrial volume index; LVDD, left ventricular diastolic dysfunction; SIS, segment involvement score; SSS, segment stenosis score; TTDE, thoracic tissue Doppler echocardiography; VFA, visceral fat area.

In this study, we observed the best relationship between EAT volume index and e′. In fact, e′ is a relatively load-independent tissue Doppler imaging measure of myocardial relaxation, which is determined by restoring forces and filling pressure, and is abnormal in any degree of diastolic dysfunction.[3] However, in the present study, nearly half of the patients without LVDD had abnormal e′, whereas the majority of these LVDD (−) patients had a normal EAT volume index, and moreover, the majority of patients with a normal EAT volume index did not have LVDD.

In our study, all of the LVDD parameters except TR velocity were significantly correlated with EAT volume index. In addition to the four LVDD parameters, Setti *et al.* demonstrated that LAVi/*a*′ is a useful marker for coupling the morphological and functional characteristics of LA and mirroring grades of LVDD, which can be applied as a potential tool to assess the diastolic function of undetermined LVDD. In line with this finding, we observed that LAVI/*a*′ was significantly associated with the EAT volume index. Whereas nearly half of the patients with no LVDD had an abnormal e′, the majority of patients with a normal EAT volume index had LVDD (−). Further studies are needed to investigate clinical utility of assessing EAT volume in combination with echocardiographic LVDD parameters to stratify patients with and without LVDD.

Atherosclerosis and LVDD

A reduction in LVDD is reportedly associated with early signs of LV function deterioration caused by myocardial ischaemia and microvascular dysfunction.[3,16] The European Society of Cardiology guidelines recommend the evaluation of LVDD as Class I in patients with suspected CAD.[1] However, the understanding of the mechanism linking coronary atherosclerosis and LVDD in patients with CCS with preserved LVEF is limited.

We found no correlation between the severity or extent of CAD and LVDD, whereas the prevalence of obstructive CAD that limits coronary flow, resulting in ischaemia, was relatively low (19–24%). This might be explained by the patient cohort in which patients with LV asynergy or LVEF < 50% were excluded. Instead, patients with LVDD had a higher %PV and CAC scores > 400 than those without LVDD. Haddad *et al.*[17] demonstrated that LVDD parameters, including e′, *E*/e′, and LV mass index, were independently associated with CAC score, even after adjusting for traditional risk factors. Although the reasons for the discordance in the association between CAC score and LVDD are unclear, different underlying mechanisms between study patients may explain the different findings. Our study population comprised patients with CCS who underwent CCTA, which may have

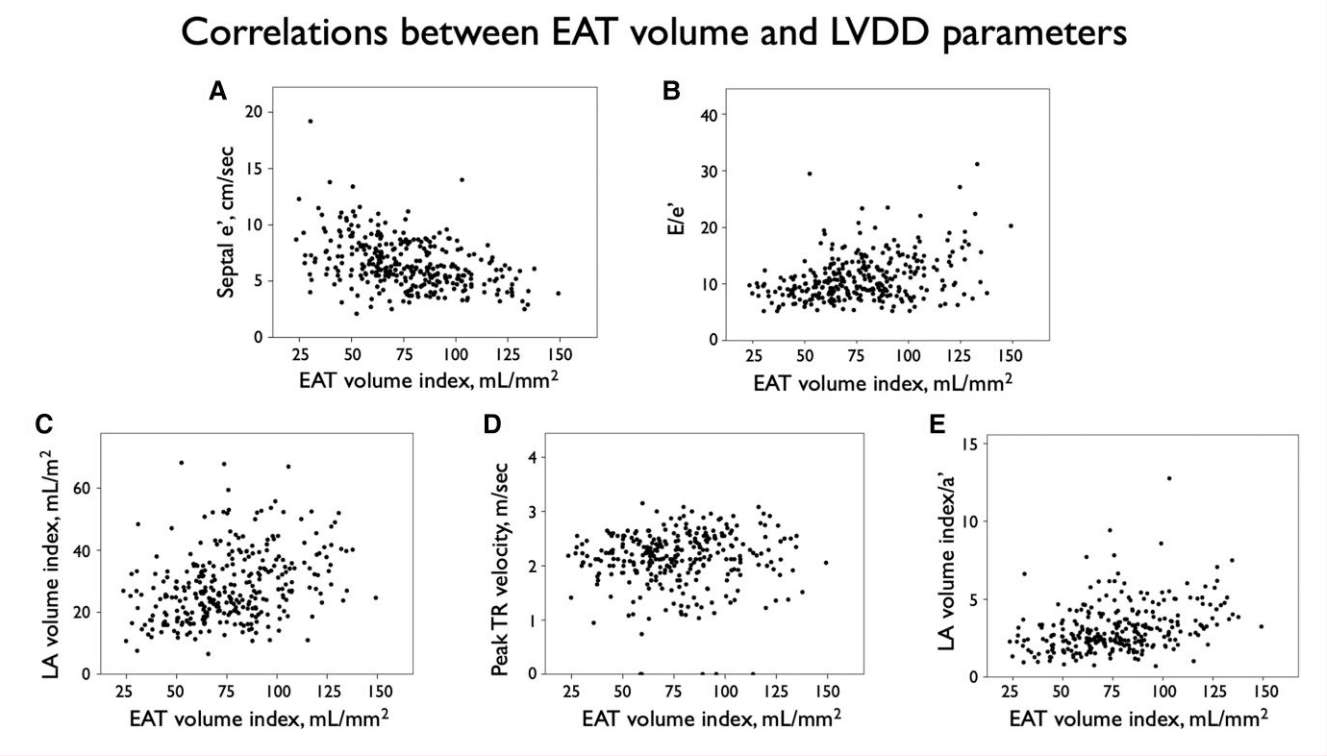


Figure 3 Correlations between EAT volume index and LVDD parameters. Correlation between septal *e'* and EAT volume index (*A*), *E*/*e'* and EAT volume index (*B*), LAVI and EAT volume index (*C*), tricuspid regurgitation peak velocity and EAT volume index (*D*), and LAVI/*a'* (*E*).

Table 3 Clinical, echocardiographic, and coronary computed tomographic angiography variables associated with left ventricular diastolic dysfunction

		Odds ratio	95% confidence interval	*P* value
Model 1	Age	1.13	1.06–1.20	<0.001
	Male	1.07	0.45–2.53	0.87
	EAT volume index	1.03	1.01–1.04	0.003
Model 2	Age	1.13	1.06–1.20	<0.001
	LV mass index	1.05	1.01–1.06	0.005
	EAT volume index	1.02	1.001–1.04	0.038
Model 3	Age	1.11	1.04–1.18	0.002
	Log (CAC score + 1)	1.18	0.97–1.43	0.102
	EAT volume index	1.03	1.01–1.04	0.005
Model 4	Age	1.11	1.04–1.18	0.003
	% total plaque volume	1.06	0.99–1.13	0.104
	EAT volume index	1.03	1.01–1.05	0.003

Model 1 was adjusted was by age and sex.
Model 2 was adjusted was by age and LVMI.
Model 3 was adjusted by age and log (CAC score + 1).
Model 4 was adjusted by age and % total plaque volume.
Age, per 1 year increase; male, yes; EAT volume index, per 1 unit increase; Log (CAC + 1), per 1 increase; %total plaque volume, per 1 unit increase
EAT, epicardial adipose tissue; LV, left ventricle.

involved more extensive coronary risk factors, including obesity. These data indicate the importance of detecting subclinical atherosclerosis to understand the link between CAD and LVDD in patients with CCS and preserved LVEF.

Clinical implications of EAT in LVDD

Obesity and ectopic adiposity are reportedly associated with HF and a preserved LVEF (ejection). EAT plays a pivotal role in cardiac fibrosis through immune cell activation.[7,8] Using cardiac magnetic resonance, Doesch *et al.*[18] demonstrated that increased EAT volume was positively correlated with worsening LV diastolic relaxation and filling in patients with cardiomyopathy. In a multivariate model, we found that increased LV mass index and EAT volume were independently associated with LVDD in our study population. In the present study, the EAT volume was correlated with each LVDD component, except for the TR velocity. This may be explained by the fact that the study population comprised patients with preserved LVEF without HF, because TR peak velocity reflects pulmonary hypertension.[2]

In a meta-analysis, Launbo *et al.*[19] demonstrated that exercise, diet, bariatric surgery, and pharmacological intervention can reduce EAT volume. In addition, recent studies have demonstrated that SGLT2 inhibitor use leads to improved LV systolic and diastolic function through the reduction of EAT and LV mass index.[20,21] These benign effects of SGLT2 inhibitors are also observed in patients with HFpEF.[22,23] Our findings suggest that increased EAT in the LVDD-undetermined group can serve as a marker of the future development of LVDD, which helps to identify individuals who will benefit from intensive medical therapy. Future studies are necessary to investigate pharmacological interventions that target EAT to prevent HF development.

Study limitations

First, this study consisted of a relatively small number of patients with preserved LVEF (>50%) without HF. Further studies are necessary to investigate whether EAT volume serves as a marker of HF development. Second, the diagnosis of LVDD was made using TTDE, and right cardiac catheterization was not performed; thus, our assessment of haemodynamic status relies on TTDE findings that are usually performed in patients with CCS. Third, we did not have data on coronary microcirculation, which may explain the link between the EAT and diastolic function in patients with preserved LVEF.

Conclusion

This study demonstrated that EAT volume index and LV mass were robust predictors of LVDD; however, there was no independent association between coronary atherosclerotic disease burden and LVDD.

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Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

Consent

All the participants provided written informed consent to participate in this study. The study was conducted in accordance with the principles of the Declaration of Helsinki. The Ethics Committee of Fujiikai Kashibaseiki Hospital, Japan approved the study protocol (Ethical Approval Number 2023–6). An opt-out process was conducted to provide patients the option to refuse or permit the use of anonymized patient data, including clinical information, laboratory test results, TTDE, and CCTA imaging.

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Conflict of interest: None declared.

Data availability

Data supporting our findings can be obtained from the corresponding author upon reasonable request.

Lead author biography

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References

1. Neumann FJ, Sechtem U, Banning AP, Bonaros N, Bueno H, Bugiardini R *et al.* 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–77.
2. Silbiger JJ. Pathophysiology and echocardiographic diagnosis of left ventricular diastolic dysfunction. *J Am Soc Echocardiogr* 2019;**32**:216–232.e2.
3. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;**29**:277–314.
4. Carroll JD, Hess OM, Hirzel HO, Turina M, Krayenbuehl HP. Left ventricular systolic and diastolic function in coronary artery disease: effects of revascularization on exercise-induced ischemia. *Circulation* 1985;**72**:119–29.
5. Ashrafpoor G, Bollache E, Redheuil A, De Cesare A, Giron A, Defrance C *et al.* Age-specific changes in left ventricular diastolic function: a velocity-encoded magnetic resonance imaging study. *Eur Radiol Germany* 2015;**25**:1077–86.
6. Bartkowiak J, Spitzer E, Kurmann R, Zürcher F, Krähenmann P, Garcia-Ruiz V *et al.* The impact of obesity on left ventricular hypertrophy and diastolic dysfunction in children and adolescents. *Sci Rep* 2021;**11**:13022.
7. Iacobellis G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol* 2022;**19**:593–606.
8. Horckmans M, Bianchini M, Santovito D, Megens RTA, Springael J-Y, Negri I *et al.* Pericardial adipose tissue regulates granulopoiesis, fibrosis, and cardiac function after myocardial infarction. *Circulation* 2018;**137**:948–60.
9. Ishikawa H, Otsuka K, Kono Y, Hojo K, Yamaura H, Hirata K *et al.* Extent of coronary atherosclerosis is associated with deterioration of left ventricular global longitudinal strain in patients with preserved ejection fraction undergoing coronary computed tomography angiography. *Int J Cardiol Hear Vasc Ireland* 2023;**44**:101176.
10. Otsuka K, Ishikawa H, Yamaura H, Hojo K, Kono Y, Shimada K *et al.* Thoracic aortic plaque burden and prediction of cardiovascular events in patients undergoing 320-row multidetector CT coronary angiography. *J Atheroscler Thromb* 2024;**31**:273–87.
11. Yamaura H, Otsuka K, Ishikawa H, Shirasawa K, Fukuda D, Kasayuki N. Determinants of non-calcified low-attenuation coronary plaque burden in patients without known coronary artery disease: a coronary CT angiography study. *Front Cardiovasc Med* 2022;**9**:824470.
12. Shmilovich H, Dey D, Cheng VY, Rajani R, Nakazato R, Otaki Y *et al.* Threshold for the upper normal limit of indexed epicardial fat volume: derivation in a healthy population and validation in an outcome-based study. *Am J Cardiol* 2011;**108**:1680–5.
13. Kuznetsova T, Thijs L, Knez J, Herbots L, Zhang Z, Staessen JA. Prognostic value of left ventricular diastolic dysfunction in a general population. *J Am Heart Assoc* 2014;**3**:1–11.
14. Lundorff IJ, Sengeløv M, Pedersen S, Modin D, Bruun NE, Fritz-Hansen T *et al.* Prognostic value of right ventricular echocardiographic measures in patients with heart failure with reduced ejection fraction. *J Clin Ultrasound* 2021;**49**:903–13.
15. Nistri S, Mazzone C, Cioffi G, Barbati G, Gentile P, Ballo P *et al.* Tissue Doppler indices of diastolic function as prognosticator in patients without heart failure in primary care. *J Cardiol Japanese Coll Cardiol* 2020;**76**:18–24.
16. Shaw LJ, Bugiardini R, Merz CNB. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009;**54**:1561–75.
17. Haddad F, Cauwenberghs N, Daubert MA, Kobayashi Y, Bloomfield GS, Fleischman D *et al.* Association of left ventricular diastolic function with coronary artery calcium score: a project baseline health study. *J Cardiovasc Comput Tomogr* 2022;**16**:498–508.
18. Doesch C, Haghi D, Flüchter S, Suselbeck T, Schoenberg SO, Michaely H *et al.* Epicardial adipose tissue in patients with heart failure. *J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson* 2010;**12**:40.
19. Launbo N, Zobel EH, von Scholten BJ, Faerch K, Jørgensen PG, Christensen RH. Targeting epicardial adipose tissue with exercise, diet, bariatric surgery or pharmaceutical interventions: a systematic review and meta-analysis. *Obes Rev an Off J Int Assoc Study Obes* 2021;**22**:e13136.
20. Iacobellis G, Gra-Menendez S. Effects of dapagliflozin on epicardial fat thickness in patients with type 2 diabetes and obesity. *Obesity (Silver Spring)* 2020;**28**:1068–74.

21. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT *et al.* Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation* 2021;**143**:516–25.
22. Akasaka H, Sugimoto K, Shintani A, Taniuchi S, Yamamoto K, Iwakura K *et al.* Effects of ipragliflozin on left ventricular diastolic function in patients with type 2 diabetes and heart failure with preserved ejection fraction: the EXCEED randomized controlled multicenter study. *Geriatr Gerontol Int* 2022;**22**:298–304.
23. Carluccio E, Biagioli P, Reboldi G, Mengoni A, Lauciello R, Zuchi C *et al.* Left ventricular remodeling response to SGLT2 inhibitors in heart failure: an updated meta-analysis of randomized controlled studies. *Cardiovasc Diabetol* 2023;**22**:235.